REMARKS

This Amendment is in response to the Office Action, dated December 3, 2009 ("Office Action"). It is respectfully submitted that the application is in condition for allowance. Claim 14 is canceled, and claims 15-19 are added. Claims 1, 3-5, 7-8, 11-13 and 15-19 are pending. No new matter has been added. Allowance and reconsideration of the application in view of Applicants' amendment and the ensuing remarks are respectfully requested.

New claims 15-19 are similar to claims 5, 7, 8, 11 and 12 with the exception that the endothelial cell does not need to be an "isolated" endothelial cell. Support for the new claims may be found throughout the specification and the original claims as filed.

The Examiner has acknowledged Applicants' petition and accepted the color drawings. Applicants thank the Examiner for the acknowledgement and acceptance.

The Examiner has also withdrawn the prior objection of claims 1 and 5; the prior §101 rejection of claims 5-8; the prior §112, second paragraph, rejection of claims 1 and 5; the prior §112, first paragraph, rejection of claims 1-8, and the prior §102(b) rejections of claims 5-8. Applicants thank the Examiner for the withdrawal of these rejections.

Claim 13 is objected to as being of improper dependent form for allegedly failing to further limit the subject matter of a previous claim for reasons of record. Applicants respectfully traverse this objection. Transdifferentiation of the monocytic cell into the endothelial cell may occur in an *in vitro* or *in vivo* environment. Thus, claim 13 further limits claim 5 by distinguishing in which environment the transdifferentiation occurs. Applicants respectfully request reconsideration and withdrawal of this objection.

Claim 14 is objected to as being of improper dependent form for failing to further limit the subject matter of a previous claim. While Applicants do not agree with the Examiner's objection, claim 14 has been canceled and thus, the objection is rendered moot.

Claim 14 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement, as allegedly containing new matter. While Applicants do not agree with the Examiner's rejection, claim 14 has been canceled and thus, the rejection is rendered moot.

Claim 1 stands and claim 11 is newly rejected under 35 U.S.C. §103(a) as being unpatentable over Havemann *et al.* (U.S. Patent Publication No. 2002/0098166) in view of Souttou *et al.* (JOURNAL OF CELLULAR PHYSIOLOGY, (2001), 187:59-64) and Powers *et al.* (JOURNAL OF BIOLOGICAL CHEMISTRY, (2002), 277(16):14153-14158) for reasons of record. Particularly, with respect to the teaching regarding PTN, the Examiner asserts that "the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of [the alternate growth factors] because the disclosure does not criticize, discredit, or otherwise discourage the solution claimed." The Examiner views Havemann *et al.* to "clearly disclose PTN as a growth factor used in the step of culturing monocytes to differentiate into endothelial-like cells or endothelial progenitor cells." The Examiner also states that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Applicants respectfully traverse this rejection.

In determining whether a claimed invention is *prima facie* obvious, the Examiner must not use impermissible hindsight; rather "the content of the prior art must be determined at the time the invention is made." MPEP §2141.01(III). Additionally, "in determining the differences between the prior art and the claims, the question...is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. MPEP §2141.02(I), emphasis in original, (citing Stratoflex, Inc., v. Aeroquip Corp., 713 F.2d 1530 (Fed. Cir. 1983). Further, "distilling an invention down to the 'gist' or 'thrust' of an invention disregards the requirement of analyzing the subject matter 'as a whole.'" Moreover, "treating the advantage as the invention disregards statutory requirement that the invention be viewed 'as a whole.'" MPEP §2141.02(II), citing W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540 (Fed. Cir. 1983) and Jones v. Hardy, 727 F.2d 1524, 1530 (Fed Cir. 1984). Additionally, "the mere fact that references can be combined or

modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art." MPEP §2143.01 (citing KSR International Co. v. Telefex Inc., 550 U.S. 398, 82 USPQ2d 1385 (2007)). As such, a "reasonable expectation of success is required." MPEP §2143.02. Furthermore, a patent cannot be relied upon to the extent that the scope of its disclosure does not reasonably suggest those aspects relied upon in the rejection. MPEP §2123 (citing Merck & Co. v. Biocraft Laboratories, 874 F.2d 804, 10USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989)).

Havemann et al. does not teach the use of PTN to obtain endothelial cells

Applicants are not attacking references individually; Applicants are disagreeing with the Examiner's erroneous interpretation of the references. The concept that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references" would be based on a premise that each individual reference indeed teaches what is alleged by the Examiner. However, when the Examiner has erroneously interpreted a prior art reference, and the erroneous interpretation is providing the basis and/or rationale for obviousness, then by attacking the Examiner's erroneous interpretation, Applicants have shown that the combination of the prior art would not be proper and thus, would not render the claimed invention obvious.

Applicants maintain that Havemann *et al.* does not reasonably teach the use of PTN to obtain endothelial cells. The Examiner erred in alleging that Havemann *et al.* "clearly" disclosed that PTN was used for differentiating the monocytic cells into endothelial cells. There is no disclosure or suggestion by Havemann *et al.* that PTN was responsible for differentiating monocytic cells into endothelial cells. The disclosure by Havemann *et al.* was in the context that the culture medium comprises "one or more of gangliosides, phospholipids, glycolipids and growth factors for endothelial cells, including factors which influence differentiation, survival, migration and vascularization." There was no suggestion or teaching of which of the "one or more of gangliosides, phospholipids, glycolipids and growth factors for endothelial cells" was actually inducing differentiation, as opposed to contributing to survival, migration or vascularization. From

Havemann *et al.*'s teaching, one of ordinary skill in the art cannot reasonably conclude that PTN was responsible for differentiating the monocytic cells into endothelial cell; it was just as likely that PTN was responsible for survival, migration and/or vascularization but not for differentiation. Havemann *et al.* is simply silent on which gangliosides, phospholipids, glycolipids or growth factors that were added to the culture media were responsible for inducing differentiation. One of ordinary skill in the art, in reading Havemann *et al.*, cannot reasonably draw a conclusion that it was PTN that was responsible for inducing differentiation. As such, Havemann *et al.* does not reasonably teach the use of PTN for differentiating monocytic cells into endothelial cells.

The Examiner appears to suggest that PTN can be used interchangeably with the other disclosed growth factors and it is simply choosing one over another to achieve the result of differentiating the monocytic cell into an endothelial cell. However, the Examiner misconstrued Havemann *et al.* to reach this conclusion. The Examiner appears to believe that Havemann *et al.* teaches that all growth factors induce differentiation. This is incorrect. At best, Havemann *et al.* teaches that the growth factors effect differentiation, survival, migration or vascularization. There is simply no teaching of which growth factor is responsible for differentiation, which growth factor is responsible for survival, which growth factor is responsible for migration and which growth factor is responsible for vascularization. Thus, it is not obvious or within the skill of one of ordinary skill in the art to conclude that PTN is responsible for differentiation without undue experimentation.

Havemann et al. in combination with Souttou et al. does not contemplate the use of PTN in a viral vector to effect transdifferentiation into an endothelial cell

Havemann *et al.*'s disclosure regarding the use of a viral vector to transform a gene encoding a growth factor to promote the endothelialization of injured vessels or angiogenesis does not contemplate the use of PTN as suggested by the Examiner. PTN was listed among the examples of growth factors that can be added to the culture media. PTN was not contemplated by Havemann *et al.* to be a gene to be expressed in its endothelial cells. Indeed, the Examiner cited paragraph 0191, which notes that among the genes to be expressed are "genes for angiogenesis factors, for example

genes for VEGF; FGF." The Examiner relied on Souttou *et al.* to state that "PTN is an angiogenic factor acting on endothelial cell proliferation, migration, survival, and capillary-like structure formation." (See August 11, 2009 Office Action, page 16, first full paragraph; emphasis added.) Applicant wishes to point out that Souttou *et al.* would thus lead one of ordinary skill in the art to believe that PTN is responsible for proliferation, migration, and survival. Turning back to Havemann *et al.*, the culture media comprise one or more of gangliosides, phospholipids, glycolipids and growth factors (e.g., PTN) for endothelial cells, including factors which influence differentiation, survival, migration and vascularization. Viewing these two articles, survival and migration are the two functions that were commonly disclosed. Thus, one of ordinary skill in the art may be led to conclude that an agent other than PTN in the culture media disclosed by Havemann *et al.* was responsible for differentiating the monocytic cells into endothelial cells. Accordingly, without a reasonable suggestion of using PTN to induce differentiation of monocytic cells, it would not have been obvious to transduce a monocytic cell with a retrovirus expressing PTN to induce differentiation.

The Examiner disregards relevant facts in the prior art of record in alleging what the references would collectively suggest

The Examiner states that obviousness is focused on what the references would collectively suggest to one of ordinary skill in the art to find obvious. However, the Examiner disregards Havemann *et al.*'s teaching of using a viral vector in endothelial cells to express a gene of interest in order to effect therapy, the Examiner disregards the fact that the monocytic cells were not transfected with the viral vector, the Examiner disregards the fact that PTN was only disclosed in the context of the culture media for the monocytic cells, and the Examiner disregards the fact that Havemann *et al.* does not teach that it is PTN that is responsible for the transdifferentiation of monocytic cells into endothelial cells. Rather, the Examiner asserts that it is the knowledge of using a viral vector to express a gene of interest in a cell that is relevant. Applicants respectfully disagree. While one of ordinary skill in the art may use a viral vector, the combination of the prior art of record does not suggest the transduction of the monocytic cell with a retrovirus expressing PTN. Havemann *et al.* teaches transducing the endothelial cell so

that the endothelial cell will express a gene of interest. As explained above, the gene of interest described by Havemann *et al.* does not include PTN. The Examiner is aware of this given the citation to Souttou *et al.* The Examiner must not ignore the fact that it is in the context of using endothelial cells that "genes for angiogenesis factors" were noted as potential effector genes (Havemann *et al.*, paragraphs 0186-0191); that is, genes that when expressed will have proteins would potentially effect therapy. The "genes for angiogenesis factors" were not disclosed in the context of transdifferentiating monocytic cells into endothelial cells. Accordingly, the combination with Souttou *et al.* for its disclosure of PTN does not teach the transdifferentiating of monocytic cells into endothelial cells. The Examiner's further citation to Powers *et al.*, for its alleged teaching that PTN has autocrine and paracrine stimulatory activities in cells expressing both PTN and PTN receptor, neither rectifies the inappropriate combination of Havemann *et al.* with Souttou *et al.*, nor adds to the rationale of how the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.* can render the claimed invention obvious. PTN's ability to have autocrine and paracrine stimulatory effect is a vast statement regarding biochemical activities. It is like stating that PTN has a biological effect. Powers *et al.* makes no recognition of PTN as being useful for differentiation, let alone for differentiation of a monocyte into an endothelial cell. Accordingly, there is no motivation to combine the Havemann *et al.* and Souttou *et al.* teachings with Powers *et al.*

The Examiner, with erroneous assumptions, is cherry picking particular disclosures using impermissible hindsight and combining them in a way that does not reasonably flow from the combined teaching of Havemann *et al.* and Souttou *et al.* Applicants understand each of the Examiner's allegations and assumptions. However, the Examiner's allegations and rationale for the rejection each rest on a faulty premise.

Thus, the combination of the prior art as a whole would not render it obvious to express PTN in a monocytic cell. There is simply no suggestion by the prior art of record to one of ordinary skill in the art, even taking into account the inferences and creative steps that one of ordinary skill would have, to transduce a monocytic cell with PTN in order to effect transdifferentiation of the monocytic cell into an endothelial cell.

The results would not have been predictable and

there would not have been a reasonable expectation of success

Applicants reiterate that the even if the references can be combined, which Applicants do not concede would be appropriate, the mere fact that they can be combined does not render the combination obvious because the results would not have been predictable to one of ordinary skill in the art and there would not be a "reasonable expectation of success" by one of ordinary skill in the art. Indeed, the Examiner still has not shown that one of ordinary skill in the art would find that using a monocytic cell (as opposed to an endothelial cell) transduced with a retrovirus expressing PTN would predictably transdifferentiate the monocytic cell into an endothelial cell. As discussed above, Havemann *et al.* made no indication on which of the "one or more of gangliosides, phospholipids, glycolipids and growth factors for endothelial cells" is responsible for differentiation of the mononuclear cells into endothelial-like cells. In its examples, only VEGF and bFGF were added in the culture media. (Havemann *et al.*, paragraphs 0247-0249.) Souttou *et al.* and Powers *et al.* do not suggest PTN as a differentiation agent. Thus, it would not be reasonably predictable to one of ordinary skill in the art that PTN alone can induce transdifferentiation of a monocytic cell into an endothelial cell.

The invention as a whole – transdifferentiation of monocytic cells into endothelial cells by transducing a retrovirus expressing PTN – would not be obvious in view of the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 3 is rejected under 35 U.S.C. §103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.*, as applied to claims 1 and 11 *supra*, and in further view of Kume *et al.* (GENE THERAPY, (2000), 7:1193-1199). The Examiner conceded that neither Havemann *et al.*, Souttou *et al.* nor Powers *et al.* teach the retrovirus expression vector to be a bicistronic retrovirus and the Examiner contended that Kume *et al.* taught the use of bicistronic retroviral vectors containing a marker gene (*e.g.*, green fluorescent protein). Thus, the Examiner concluded that it

would have been obvious to one of ordinary skill in the art to substitute the retroviral expression vector by Havemann *et al.* with a bicistronic retroviral expression as taught by Kume *et al.* Applicants respectfully traverse this rejection.

Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.* and Kume *et al.* would not render claim 3 obvious. For all the reasons discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 1 obvious because, among other things, (1) one of ordinary skill in the art would not interpret Havemann *et al.* in the manner interpreted by the Examiner, (2) one of ordinary skill in the art would not combine these teachings, and (3) there is no predictability or expectation of success for the transduced monocytic cell to transdifferentiate into an endothelial cell based on the combination. Since claim 3 depends from claim 1, it would similarly not be obvious as the determination of obvious of the claim also requires, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same expectation of success. Since there is no predictability and no expectation of success from the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.*, there will not be any predictability or expectation of success for the combination of Havemann *et al.* Souttou *et al.*, Powers *et al.* and Kume *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 4 is rejected under 35 U.S.C. §103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.* and Kume *et al.*, as applied to claims 1, 3, and 11 *supra*, and in further view of Pufe *et al.*, Howett *et al.* (U.S. PATENT No. 6,309,848) and Eslami *et al.* (JOURNAL OF VASCULAR SURGERY, (2001). 34:923-929). The Examiner conceded that neither Havemann *et al.*, Souttou *et al.*, Powers *et al.*, nor Kume *et al.* teach the monocytes to be THP-1 monocytes. However, the Examiner contended that THP-1 cells are taught by Pufe *et al.* as being responsive to PTN stimulation; by Howett *et al.* as being useful for implantation; and by Eslami *et al.* as being capable of binding to injured human vein grafts. The Examiner concluded that it

would have been obvious to one of ordinary skill in the art to substitute a first mononuclear/monocytic cell as taught by Havemann *et al.* with a second monocytic cell (specifically, THP-1) as taught by Pufe *et al.* Applicants respectfully traverse this rejection.

Applicants again suspect and submit that Kume *et al.* was erroneously applied to the rejection of claim 4. The Examiner has applied Kume *et al.* to reject claim 3; however, claim 4 does not depend from claim 3. As such, Kume *et al.* does not appear to be applicable to claim 4. Applicants request clarification regarding Kume *et al.* Nonetheless, Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* would not render claim 4 obvious. As discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 1 obvious because, among other things, (1) one of ordinary skill in the art would not interpret Havemann *et al.* in the manner interpreted by the Examiner, (2) one of ordinary skill in the art would not combine these teachings, and (3) there is no predictability or expectation of success for the transduced monocytic cell to transdifferentiate into an endothelial cell based on the combination. Since claim 4 depends from claim 1, it would similarly not be obvious as the determination of obviousness of the claim also requires, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same expectation of success. Since there is no predictability and no expectation of success from the combination of Havemann *et al.*, Souttou *et al.*, and Powers *et al.*, there will not be any predictability or expectation of success for the combination of Havemann *et al.* Souttou *et al.* Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett

et al. and Eslami *et al.* as applied to Claims 1, 3-4 and 11 *supra*, and in further view of Kawamoto *et al.* (Circulation 103:634-637, 2001) for reasons of record. Particularly, the Kawamoto *et al.* taught *in vivo* transplantation of endothelial progenitor cells obtained from mononuclear cells, and isolated tissue comprising endothelial cells that had transdifferentiated from said mononuclear cells *in vivo*." Applicants respectfully traverse this rejection.

It appears the Examiner has mistakenly applied Kume *et al.*, Pufe *et al.*, and Howett *et al.* to claim 12 because claim 12 is only dependent on claim 1. Clarification from the Examiner is requested. Regardless, Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, and Howett *et al.* does not render obvious the use of a retroviral expressing PTN to induce differentiation of the monocytic cells into endothelial cells as discussed in detail above. Thus, the combination including Kawamoto *et al.* does not render it obvious to first transduce a retrovirus expressing PTN into the monocytic cell to induce differentiation into an endothelial cells and then allow the differentiation to occur *in vivo*. In light of the above, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claims 5 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.* for reasons of record. Particularly with respect to *in vitro* differentiation, the Examiner finds that Havemann *et al.* discloses that "the isolated mononuclear cells are cultured and differentiated to give endothelial-like cells *in vitro*." Applicants respectfully traverse this rejection.

As discussed above, the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.* does not render obvious a method of transdifferentiating a monocytic cell into an endothelial cell by transducing the monocytic cell with a retrovirus expressing PTN. Accordingly, for the same reasons, Havemann *et al.*, Souttou *et al.* and Powers *et al.* does not render obvious an isolated endothelial cell produced by the same method. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.* and Powers *et al.*, as applied to Claims 5 and 13 *supra*, and in further view of Kume *et al.* for reasons of record. Applicants respectfully traverse this rejection.

Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*, Powers *et al.* and Kume *et al.* would not render claim 7 obvious. As discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 5 or 13 obvious because the combination does not render obvious a method of transdifferentiating a monocytic cell into an endothelial cell by transducing the monocytic cell with a retrovirus expressing PTN, and therefore would not render obvious an isolated endothelial cell produced by the same method. Since claim 7 depends from claim 5, all the reasons apply and it would similarly not be obvious as the determination of obviousness of the claim also requires, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same expectation of success. Since there is no predictability and no expectation of success from the combination of Havemann *et al.*, Souttou *et al.* and Powers *et al.*, there will not be any predictability or expectation of success for the combination of Havemann *et al.* Souttou *et al.*, Powers *et al.* and Kume *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, and Kume *et al.* as applied to Claims 5, 7, and 13 *supra*, and in further view of Pufe *et al.*, Howett *et al.*, and Eslami *et al.* for reasons of record. Applicants respectfully traverse this rejection.

Applicants again suspect and submit that Kume *et al.* was erroneously applied to the rejection of claim 8. The Examiner has applied Kume *et al.* to reject claim 7; however, claim 8 does not depend from claim 7. As such, Kume *et al.* does not appear to be applicable to claim 8. Applicants request clarification regarding Kume *et al.* Nonetheless, Applicants submit that the combination of Havemann *et al.*, Souttou *et al.*,

Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* would not render claim 8 obvious. As discussed above, the combination of Havemann *et al.* Souttou *et al.* and Powers *et al.* would not render claim 5 obvious, because, among other things, there would not be any expectation of success. Since claim 8 depends from claim 5, it would similarly not be obvious as the determination of obviousness of the claim also requires, among other things, the predictability that a monocytic cell transduced with a retrovirus expressing PTN would transdifferentiate into an endothelial cell and the same expectation of success. Since there is no predictability and no expectation of success from the combination of Havemann *et al.*, Souttou *et al.*, and Powers *et al.*, there will not be any predictability or expectation of success for the combination of Havemann *et al.* Souttou *et al.* Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.*; although Applicants do not concede that it is proper to combine Kume *et al.*, Pufe *et al.*, Howett *et al.* and Eslami *et al.* with Havemann *et al.*, Souttou *et al.*, and Powers *et al.* In light of the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection under §103(a).

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, Howett *et al.*, and Eslami *et al.*, as applied Claims 1, 3-4 and 11 *supra*, and in further view of Kawamoto *et al.* for reasons of record. Particularly, the Examiner finds that "to the extent that the claims are drawn to an isolated endothelial cell that transdifferentiated from a monocyte *in vivo*, and the specification discloses figures of isolated tissue comprising said endothelial cell that transdifferentiated from a monocyte *in vivo* (Figures 5A-H), the Examiner interprets isolated tissue comprising endothelial cell(s) that transdifferentiated from a monocyte *in vivo* to fulfill the limitations of the claim. "The Examiner further finds that Kawamoto *et al.* taught *in vivo* transplantation of endothelial progenitor cells obtained from mononuclear cells, and isolated tissue comprising endothelial cells that had transdifferentiated from said mononuclear cells *in vivo*." Applicants respectfully traverse this rejection.

Claim 12, depending from claim 1, is directed to a method of transdifferentiating a monocytic cell into an endothelial cell. There is no limitation of an "isolated"

endothelial cell in claim 12. Thus, Applicants do not agree with the Examiner's interpretation of the claim and are confused as to the Examiner's interpretation of the claim. Further, it appears the Examiner has mistakenly applied Kume *et al.*, Pufe *et al.*, and Howett *et al.* to claim 12 because claim 12 is only dependent on claim 1. Clarification from the Examiner is requested.

Regardless, Applicants submit that the combination of Havemann *et al.* in view of Souttou *et al.*, Powers *et al.*, Kume *et al.*, Pufe *et al.*, and Howett *et al.* do not teach the use of a retroviral expressing PTN to induce differentiation of the monocytic cells into endothelial cells as discussed in detail above. Thus, the combination including Kawamoto *et al.* does not render it obvious to first transduce a retrovirus expressing PTN into the monocytic cell to induce differentiation into an endothelial cells and then allow the differentiation to occur *in vivo*. In light of the above, Applicants respectfully request reconsideration and withdrawal of this rejection.

Applicants suspect that the Examiner may have intended to reject claim 14. If this was the Examiner's intention, Applicants still respectfully traverse the rejection. While Applicants in no way concede to the merits of the Examiner's rejection, claim 14 has been canceled, and thus, this rejection is rendered moot.

In the interest of advancing prosecution, Applicants offer the following comments regarding new claims 15-19. Applicants note that claim 15 is produced by transducing the monocytic cell with a retrovirus expressing PTN. Such an endothelial cell does not exist in nature. Thus, the endothelial cell is can be regarded as "by hand of man" and is thus, patentable subject matter.

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All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,
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